CLAIMS

1. Isolated polypeptide, characterized in that it makes it possible to restore a deficient KAR activation, or a fragment or homologue of such a polypeptide.

2. Polypeptide according to claim 1, characterized in that it is capable of associating with a KAR and not associating with the inhibitory counterpart of this KAR, or a fragment or homologue of such a polypeptide.

3. Polypeptide as obtained:

i. by immunoprecipitation of one or more polypeptide fractions of lysates of cells expressing KAR receptors capable of transducing an activating signal, with one or more anti-KIR and/or anti-KAR antibodies such as an anti-CD158, anti-p70/NKB1 or anti-p140 antibody and more particularly the EB6, GL183 or PAX250 monoclonal antibody,

ii. it optionally being possible for each polypeptide fraction to be exhausted beforehand by removal of the fractions immunoprecipitated with anti-CD3 and/or anti-FcεRIγ antibodies, and/or to be reprecipitated with one or more anti-KIR and/or anti-KAR antibodies such as an anti-CD158, anti-p70/NKB1, anti-p140 antibody and more particularly the EB6, GL183 or PAX250 monoclonal antibody,

iii. by resolution of the polypeptides of said polypeptide fraction(s) according to their molecular weight, and recovery of the polypeptides corresponding to a molecular weight of about 12 ± 2 kDa, or

by resolution of the polypeptides of said polypeptide fraction(s) according to their molecular weight after said polypeptide fraction(s) has (have) been subjected to a kinase test, and recovery of the phosphorylated polypeptides corresponding to a molecular weight of about 12, 14 and/or 16 ± 2 kDa,
or a fragment or homologue of such a polypeptide.

4. Polypeptide according to claim 3, characterized in that said cells are NK cells and/or T cells and/or myeloid cells and/or B cells and/or mastocytes.

5. Polypeptide according to any one of the preceding claims, characterized in that its amino acid sequence:

- has at least one phosphorylatable tyrosine amino acid, and
- has a molecular weight of between about 10 ± 2 and 16 ± 2 kDa.

6. Polypeptide according to any one of the preceding claims, characterized in that its amino acid sequence contains at least one ITAM YxxL/Ix_{6-8}YxxL/I.

7. Polypeptide according to any one of the preceding claims, characterized in that its amino acid sequence contains an extracytoplasmic region, a transmembrane region and an intracytoplasmic region.

8. Polypeptide according to any one of the preceding claims, characterized in that its amino acid sequence contains at least one extracytoplasmic cysteine amino acid.

9. Polypeptide according to any one of the preceding claims, characterized in that its amino acid sequence contains at least one transmembrane charged amino acid (R, K, D, E).

10. Polypeptide according to any one of the preceding claims, characterized in that it is phosphorylated on at least one tyrosine residue.

11. Polypeptide according to any one of the preceding claims, characterized in that it is in the form of dimers.

12. Polypeptide according to any one of the preceding claims, characterized in that it binds to a molecule having an SH2 or PTB domain.

13. Polypeptide according to any one of the preceding claims, characterized in that its amino acid sequence essentially consists of SEQ ID no. 2, no. 3, no. 4, no. 5, no. 11, no. 12, no. 13, no. 14, no. 15, no. 17 or no. 28.

14. Polypeptide according to any one of the preceding claims, characterized in that it is modified by glycosylation, phosphorylation, sulphonation, biotinylation, acylation or esterification, by the addition, substitution or suppression of entities whose molecular shape is similar to that of phosphate groups, such as phosphonate, by the addition of tracer reagents such as luciferase, GFP (*Green Fluorescence Protein*) or analogues thereof, by the addition of purification targets such as an affinity ligand, or by the addition of entities modifying its solubility.

15. Polypeptide according to any one of the preceding claims, characterized in that it is capable of crossing a cell membrane.

16. Polypeptide according to any one of the preceding claims, characterized in that it is modified so as to inhibit its capacity to transduce a signal.

17. Polypeptide according to claim 17, characterized in that it is modified so as to be non-hydrolyzable under biological conditions, especially by the addition of phosphonate groups.

18. Polypeptide according to claim 17, characterized in that it is modified by substitution of a tyrosine residue with a phenylalanine residue.

19. Antibody or fragment of such an antibody, particularly an Fc, Fv, Fab, F(ab)'2 or CDR fragment, as obtained by immunogenesis from a polypeptide according to any one of the preceding claims or from a fragment of such a polypeptide.

20. Antibody or antibody fragment according to claim 20, characterized in that it is capable of recognizing SEQ ID no. 2, SEQ ID no. 3, SEQ ID no. 4, SEQ ID no. 5, SEQ ID no. 11, SEQ ID no. 12, SEQ ID no. 13, SEQ ID no. 14, SEQ ID no. 15, SEQ ID no. 17 and/or SEQ ID no. 28.

21. Nucleic acid or variant of such a nucleic acid, characterized in that it comprises a sequence corresponding to the open reading frame, according to the universal genetic code, of the amino acid sequence of a polypeptide according to any one of the preceding claims.

22. Nucleic acid according to claim 22, or variant of such a nucleic acid, characterized in that said nucleic acid has a sequence essentially consisting of SEQ ID no. 2, no. 6, no. 7, no. 8, no. 9, no. 10, no. 16, no. 27, no. 31 or no. 18.

23. Process for obtaining a polypeptide according to any one of the preceding claims, characterized in that it comprises steps involving:

i. immunoprecipitation of one or more polypeptide fractions of lysates of KAR^+ cells with one or more anti-KIR and/or anti-KAR antibodies such as an anti-CD158, anti-p70/NKB1 or anti-p140 antibody and more particularly the EB6, GL183 or PAX250 monoclonal antibody,

ii. it optionally being possible for each polypeptide fraction to be exhausted beforehand by removal of the fractions immunoprecipitated with anti-CD3 and/or anti-FcεRIγ antibodies, and/or to be reprecipitated with one or more anti-KIR and/or anti-KAR antibodies such as an anti-CD158, anti-p70/NKB1 or anti-p140

antibody and more particularly the EB6, GL183 or PAX250 monoclonal antibody, and

iii. separation of the polypeptides of said polypeptide fraction(s) according to their molecular weight, and recovery of the polypeptides corresponding to a molecular weight of about 12 ± 2 kDa, or

separation of the polypeptides of said polypeptide fraction(s) according to their molecular weight after said polypeptide fraction(s) has (have) been subjected to a kinase test, and recovery of the phosphorylated polypeptides corresponding to a molecular weight of about 12, 14 and/or 16 ± 2 kDa.

24. Process according to claim 23, characterized in that said KAR^+ cells are NK cells and/or T cells and/or myeloid cells and/or B cells and/or mastocytes.

25. Method of obtaining the sequence of a polypeptide according to any one of Claims 1 to 18, characterized in that it is carried out by screening candidate sequences so as to select only that (those) which:

- has (have) at least one phosphorylatable tyrosine amino acid,
- has (have) a molecular weight of between about 5 and 25 kDa,
- contains (contain) an extracytoplasmic region, a transmembrane region and an intracytoplasmic region,
- contains (contain) at least one cysteine amino acid in its extracytoplasmic region,
- contains (contain) at least one charged amino acid (R, K, D, E) in its transmembrane region, and
- contains (contain) at least one ITAM $YxxL/Ix_{6-8}YxxL/I$ in its intracytoplasmic region,

and in that it is ensured that the polypeptide(s) corresponding to the selected sequence(s) is (are) capable of associating with a KAR receptor while at the same time not associating with the counterpart receptor which inhibits this KAR.

26. Method of determining whether a candidate polypeptide corresponds to a polypeptide according to any one of Claims 1 to 18, characterized in that it comprises:

- producing a monoclonal or polyclonal antibody directed against this candidate polypeptide and in particular against an extracytoplasmic region of this candidate polypeptide and/or a region comprising at least one ITAM unit,
- bringing this antibody into contact with a lysate of cells possessing, in a functional form, the activating or non-inhibitory receptor for which the candidate

polypeptide is assumed to constitute the KARAP, under mild conditions allowing binding reactions of the antigen-antibody type,

- identifying the candidate polypeptide as being a polypeptide according to any one of Claims 1 to 18 when the reaction products which may be formed contain a product whose apparent molecular weight is similar to that of said activating or non-inhibitory receptor, and a product whose apparent molecular weight is similar to that of the candidate polypeptide.

27. Pharmaceutical composition comprising, in association with a pharmaceutically acceptable vehicle, an effective amount of polypeptides according to any one of the preceding claims, or fragments of such polypeptides, or an effective amount of antibodies according to claim 19 or 20, or fragments of such antibodies, or an effective amount of nucleic acids according to claim 21 or 22, or variants of such nucleic acids.

28. *In vitro* method of diagnosing an abnormal or undesired function of a cell, characterized in that it comprises steps involving:

- bringing of at least one cell, or one cell extract, into contact with an antibody according to claim 21 or 22, or a fragment of such an antibody, or with a nucleic acid according to claim 21 or 22, or a variant of such a nucleic acid, and
- revealing of the reaction product which may be formed.

29. *In vitro* diagnostic method according to claim 28, characterized in that said abnormal or undesired function results in an immunoproliferative disease, an immunodeficiency disease such as an HIV disease, a cancer such as lymphoproliferative disease of the granular lymphocytes, an autoimmune disease such as rheumatoid arthritis, an infectious disease such as malaria, an allergic response or a graft reject.

30. Method of identifying molecules which adapt or carry out the activation of a KAR, characterized in that it comprises steps involving:

i. bringing of the candidate molecules into contact with polypeptides according to any one of Claims 1 to 18 (or with fragments of such polypeptides), and

ii. selection of those candidate molecules for which a binding to said polypeptides (or to said polypeptide fragments) is observed.

31. Method of identifying molecules capable of modulating a cell activity resulting from the activation of a KAR, characterized in that it comprises steps involving:

i. bringing of the candidate molecules into contact with molecules which adapt or carry out the activation of a KAR, as obtained by the method according to claim 30, and with polypeptides according to any one of claims 1 to 18 (or with fragments of such polypeptides), and

ii. selection of those candidate molecules which exert an effect on the binding between said polypeptides (or said polypeptide fragments) and said adapter or effector molecules, as observed in the absence of said candidate molecules.